PATENT
Customer No. 22,852
Attorney Docket No. 09487.0001-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Timothy G. DINAN et al.	Group Art Unit: 1614
Application No.: 09/687,384	Examiner: Donna A. JAGOE
Filed: October 13, 2000	
For: TREATMENT AND PREVENTION OF GASTROINTESTINAL DISEASE USING ANTAGONISTS OR PARTIAL AGONISTS OF 5HT1a RECEPTORS	Confirmation No.: 7338

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF UNDER BOARD RULE § 41.37

In support of the Notice of Appeal filed June 28, 2004, and further to Board Rule 41.37, Appellants present this brief and enclose herewith a check for the fee of $500.00 required under 37 C.F.R. § 1.17(c).

This Appeal Brief is being filed concurrently with a Petition for an Extension of Time for five-months, and the appropriate fee. This Appeal responds to the February 26, 2004, final rejection of claims 1 and 4-7.

If any additional fees are required or if the enclosed payment is insufficient, Appellants request that the required fees be charged to Deposit Account No. 06-0916.

Real Party In Interest

AGI Therapeutics Ltd. is assignee of record, as evidenced by the assignment document filed in the U.S. Patent and Trademark Office on August 20, 2004, and recorded at Reel 015076 and Frame 0001.

Related Appeals and Interferences

There are currently no other appeals or interferences, of which Appellants, Appellants' legal representative, or Assignee are aware, that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

Status Of Claims

Claims 1 and 4-7 stand rejected and are being appealed. Claims 2-3 are canceled. A complete listing of the pending claims is included in the attached appendix, entitled "Claims Appendix to Appeal Brief Under Rule 41.37(c)(1)(viii)."

Status Of Amendments

An Amendment and Request for Reconsideration under 37 C.F.R. § 1.116 was filed on May 6, 2004, subsequent to the Final Office Action dated February 26, 2004, but not entered for the purposes of Appeal, as evidenced in the Advisory Action dated June 1, 2004. In addition, a Second Amendment and Request for Reconsideration under 37 C.F.R. § 1.116 was filed on June 28, 2004, in response to the Advisory Action, dated June 1, 2004. The Second Amendment and Request for Reconsideration was not entered for the purposes of Appeal, as evidenced by the Advisory Action dated January 18, 2005. Copies of the Amendments dated May 6, 2004, and June 28, 2004, are included in the Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix).

Summary Of Claimed Subject Matter

Pindolol is a beta-adrenergic antagonist used in the treatment of hypertension and angina. Specification at page 5, ll. 15-16. Pindolol also has affinity for 5HT1a receptors similar in magnitude to its affinity for beta-adrenergic receptors. *Id.* at page 5, ll. 16-17. From various studies, the 5HT1a receptors may be involved in the pathophysiology of idiopathic or nonulcer dyspepsia (NUD). *Id.* at page 3, ll. 14-15. NUD consists of chronic or recurrent upper abdominal pain or discomfort in the absence of obvious pathology. *Id.* at page 2, ll. 22-24.

Accordingly, the present invention provides for a method of treatment comprised of administering a composition consisting essentially of S(-) pindolol or salts thereof to reduce the sensitivity of 5HT1a receptors and as a result, to provide for treatment of certain gastrointestinal diseases, including non-ulcerative dyspepsia. *Id.* at page 5, ll. 20-24; *see also*, independent claim 1.

Grounds of Rejection

Claims 1 and 4-7 stand rejected under 35 U.S.C. § 103(a) as unpatentable over RO 92436 to Buzas et al. ("Buzas").

Argument

CLAIMS 1 AND 4-7 ARE PATENTABLE UNDER 35 U.S.C. § 103(a) OVER RO 92436 TO BUZAS ET AL.

A. The Office fails to establish a prima facie case of obviousness

1. The criteria for making a prima facie case of obviousness are clearly set forth in the M.P.E.P. and in case law.

To establish a prima facie case of obviousness, the Office must meet three basic criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143 (8th ed. Rev. 2, 2004).

"The examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness." M.P.E.P. § 2142. In doing so, "all the words in a claim must be considered in judging the patentability of the claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Further, it is not sufficient to merely "find every element of a claimed invention in the prior art [and for] an examiner to use the claimed invention itself as a blue print for piecing together elements . . . Such an approach would be an illogical and inappropriate process by which to determine patentability." *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457 (Fed. Cir. 1998) (citations and quotations omitted). Instead, the art must suggest the desirability of the modifications. *See In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q.2d 1125, 1127 (Fed. Cir. 1984) ("The mere fact that the prior art could be so modified

would not have made the modification obvious unless the prior art suggested the desirability of the modification.").

2. The criteria have not been met by the rejection of record.

The Office asserts that Buzas teaches a composition comprising a carbonic anhydrase inhibitor and a beta-blocker such as pindolol to treat gastritis, gastro-duodenitis, and gastro-duodenal ulcers. Office Action dated August 14, 2003, at page 6. The Office concedes that Buzas does not teach S(-)pindolol, but asserts that "since it is known that pindolol is an antagonist of 5HT1a, it is reasonable to expect that S(-)pindolol would also have those properties." *Id.* According to the Examiner, the "comprising" language used in Applicants' originally filed claims does not exclude the combination of carbonic anhydrase inhibitors with pindolol and Buzas therefore renders those claims obvious. Office Action dated February 26, 2004, at page 3.

Appellants subsequently amended the claims to exclude the synergistic combination of pindolol with carbonic anhydrase inhibitors by changing the "comprising" transitional phrase to "consisting essentially of." Amendment filed May 6, 2004. The Office, however, contends that the addition of the carbonic anhydrase inhibitor of Buzas would not *materially* change the characteristics of Appellants' pindolol composition and that the teachings in Buzas continue to render obvious the presently claimed invention. Advisory Action dated June 1, 2004. In addition, the Office now asserts that because synergy means "the interaction of two or more treatments such that their combined effect is greater than the sum of the individual effects observed when each treatment is administered alone," Buzas teaches that pindolol used alone can treat gastrointestinal

disease, but has a greater effect when administered together with a carbonic anhydrase inhibitor. Advisory Action dated January 18, 2005. Appellants respectfully disagree.

Appellants submit that, among other things, the transitional phrase "consisting essentially of" excludes compounds such as the carbonic anhydrase inhibitors taught in Buzas that produce a synergistic effect when combined with S(-) pindolol and, furthermore, that there is no suggestion or motivation to modify the teachings of Buzas to omit the carbonic anhydrase inhibitor. Accordingly, Appellants respectfully request reversal of the rejection of the record.

3. *Including a carbonic anhydrase inhibitor would lead to a material change in the presently claimed composition.*

The transitional phrase "consisting essentially of" renders a claim open for the inclusion of only unspecified ingredients that do not "*materially affect* the basic and novel characteristics of the claimed composition." *Dow Chemical Co. v. American Cyanamid Co.*, 615 F. Supp. 471, 484, 229 U.S.P.Q. 171, 180 (E.D. La. 1985), *aff'd*, 816 F.2d 617, 2 U.S.P.Q.2d 1350 (Fed. Cir. 1987) (emphasis added). The "consisting essentially of" claim occupies middle ground between the closed transitional phrase "consisting of" and the open transitional phrase "comprising." *See* M.P.E.P. § 2111.03.

The Federal Circuit discussed in *PPG Industries v. Guardian Industries Corp.*, 156 F.3d 1351, 48 U.S.P.Q.2d 1351 (Fed. Cir. 1998), *inter alia*, what constitutes a "material effect." The claim of interest read:

> A green tinted, ultraviolet absorbing glass having a base glass composition consisting essentially of . . . and a colorant portion consisting essentially of [ferrous or ferric iron and cerium oxide].

Guardian argued that its glass did not infringe because it contained iron sulfide, which was not listed as a colorant in PPG's patent. *Id.* at 1353, 48 U.S.P.Q.2d at 1353. PPG argued that iron sulfide was an inherent by-product of the float glass manufacturing process used by both Guardian and PPG. *Id.* at 1354, 48 U.S.P.Q.2d at 1353. PPG also pointed to a passage in the specification that stated "[m]elting and fining aids such as SO_3 are useful during production of the glass, but their residual amounts in the glass may vary and have no significant effect on the properties of the glass product." *Id.* at 1355-56, 48 U.S.P.Q.2d at 1355.

The Federal Circuit held that there was substantial evidence from which the jury could conclude that the iron sulfide in the glass had a material effect on the basic and novel properties of the glass. *Id.* at 1357, 48 U.S.P.Q.2d at 1356. Under this holding, the court highlighted evidence indicating that those skilled in the art would regard even small changes in the color or transmittance of tinted glass to be material; measurable, reproducible changes that cannot be attributed to experimental error. *Id.* at 1357, 48 U.S.P.Q.2d at 1357. Thus, despite the specification generally suggesting that sulfur compounds have insignificant effects on the properties of the glass, the court found that sulfur in the glass in the form of iron sulfide is a strong colorant and that even small changes in color are material parameters important to the skilled artisan.

In *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 68 U.S.P.Q.2d 1280 (Fed. Cir. 2003), the patent of interest covered hot dip aluminum-coated stainless steel and the issue was whether an amount of silicon in excess of 0.5% in the aluminum coating materially affected the basic and novel properties of the invention. 344 F.3d at 1236, 1239, 68 U.S.P.Q.2d at 1282, 1283. In this case, the specification of the patent of interest was

far from silent with regard to silicon's affect on the properties of the aluminum coating bath and the resultant coated steel. *Id.* at 1240, 68 U.S.P.Q.2d at 1283-84. As the Federal Circuit explained, the patent expressly provided that the silicon content should not exceed 0.5% or the aluminum coating would not adhere well to steel. *Id.*, 68 U.S.P.Q.2d at 1284. Despite AK Steel's attempt to argue that the statements in the specification were merely explaining a scientific theory and as such, should not be used to limit the claimed invention, the court indicated that conclusions speaking to the conditions under which the invention will or will not operate are not theory and thus, impact the meaning of the claim phrase "consisting essentially of aluminum." *Id.*, 68 U.S.P.Q.2d at 1284. Accordingly, the specification directly spoke to the effects of silicon on the properties of aluminum coating bath, and the court held as a mater of claim construction that the claims do not encompass steel coated with aluminum containing more than about 0.5% silicon.

Applying these cases to the current situation, one should at least look to the present specification to determine what Appellants consider to materially affect the basic and novel properties of the present invention. Although the specification lacks a definitive statement with regard to carbonic anhydrase inhibitors as in *AK Steel*, Appellants submit that on page 4, lines 14-17 of the specification, an aspect of the present invention, is "the administration of effective amounts of a substance" leading to beneficial effects in subjects suffering from non-ulcerative dyspepsia. As such, the question is whether the addition of a carbonic anhydrase inhibitor taught in Buzas to a composition of pindolol would have a material effect on the basic and novel

characteristics of the claimed method. To answer this question, one need only look no further than the disclosure in Buzas.

Buzas teaches that carbonic anhydrase inhibitors, when used in combination with certain other specified compounds (including some beta-blockers like pindolol), provide a *synergistic* effect. Synergistic effects "demonstrate 'an effect greater than the sum of the several effects taken separately.'" *Merck & Co. v. Biocraft Labs, Inc.*, 874 F.2d 804, 808, 10 U.S.P.Q.2d 1843 (Fed. Cir. 1989). In fact, "synergism may point toward nonobviousness . . . ." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1540, 218 U.S.P.Q. 871, 880 (Fed. Cir. 1983) (explaining that synergism is not a requirement under an obviousness inquiry, but indicates nonobviousness). Given that synergistic effects, when present, point to nonobviousness, these effects are material.

Buzas' synergistic compositions contain a carbonic anhydrase inhibitor and a beta-adrenergic blocker selected from among propranolol, atenolol, pindolol, timolol, oxprenolol, acebutolol, or metoprolol in a weight ratio in the range of 1.37 to 231. Buzas et al. Translation at page 2 (The Buzas et al. Translation was submitted to the Office with the Response filed on November 13, 2003, and a copy of the translation can be found in the evidence appendix). Buzas states that "[t]he object of the present invention is to obtain a *synergistic* pharmaceutical composition . . . [through the] selection of ingredients and the mixture ratio thereof." *Id.* (emphasis added). Each of Buzas' claims is also explicitly limited to "synergistic" combinations. "[A] reference must be considered for not only what it expressly teaches, but also for what it fairly suggests." *In re Burckel*, 592 F.2d 1175, 1179, 201 U.S.P.Q. 67, 70 (C.C.P.A. 1979). Thus, achieving synergy appears to be Buzas' whole basis for describing the use of such combination therapies.

Nevertheless, the Office contends that Buzas "fairly suggests" that beta-blockers used alone produce therapeutic effects on gastrointestinal disorders.

In fact, Buzas presents evidence confirming that beta-blockers used *alone* are not effective agents for treating gastrointestinal disorders. Buzas et al. Translation at page 8, Table 3. For example, Buzas measured the production of hydrochloric acid and the activity of carbonic anhydrase in human gastric mucosa and in red blood cells in patients with duodenal ulcers. *Id.* The results below, which are from Buzas, show that pindolol used alone did not differ from a control with respect to hydrochloric acid flow. In addition, Buzas observed no difference between the effect of pindolol and a control on carbonic anhydrase activity in gastric mucosa cells and in red blood cells.

Beta-blocker	**Hydrochloric Acid Flow (mEq/h)**	**Carbonic Anhydrase Activity in Gastric mucosa Cells**	**Carbonic Anhydrase Activity in Red Blood Cells**
Control	9.87 ± 2.71	1.87 ± 0.13	2876 ± 139
Pindolol	7.98 ± 1.17	1.70 ± 0.31	2590 ± 113

Id. at page 8, Table 3.

Based on other data, Buzas concludes that "*[i]n vivo* administration of carbonic anhydrase inhibitors and *beta*-adrenergic blockers to patients with gastroduodenal disorders has therapeutic effects (reduced secretion parameters) and leads to healing using reduced [carbonic anhydrase] inhibitor doses (table 9)." Buzas et al. Translation at page 11. The results summarized below clearly demonstrate the *synergistic* action identified by Buzas.

Name	Hydrochloric Acid Flow (mEq/h)	Carbonic Anhydrase Activity
Control	9.87 ± 2.71	76 ± 22
Ethoxzolamide	3.87 ± 0.98	37 ± 17
Pindolol	7.98 ± 2.17	69 ± 22
Ethoxzolamide + Pindolol	0.71 ± 0.17	24 ± 3

Id. at page 12, Table 9. A comparison of the combination of compounds to those compounds used alone demonstrates a significant increase of the activity of the combination compared to either compound alone. Thus, the combination of a carbonic anhydrase inhibitor and pindolol is not merely additive but instead, produces a greater effect on the tested parameters than predicted from the activity of either compound individually.

Despite this evidence, the Office contends that because the combination of pindolol with a carbonic anhydrase inhibitor is synergistic, Buzas suggests that "the beta-adrenergic blocker, such as pindolol, administered alone is *effective* in treating gastrointestinal disease, and when combined with the carbonic anhydrase inhibitor, the net effect is greater than when one agent is administered alone." Advisory Action dated January 18, 2005 (emphasis added). For the reasons above, Buzas' data "fairly suggests" quite the opposite.

There simply is no rational basis for the Office's conclusion, which appears to be grounded in a definition of synergy as "the interaction of two or more treatments such that their combined effect is greater than the sum of the individual effects observed

when each treatment is administered alone." But, despite the Office's position, nothing in this definition requires that any component of a synergistic composition by itself produce a therapeutic effect as required by the rejected claims.

As in *PPG Industries*, Buzas' specification and data provide evidence from which a skilled artisan would conclude that adding a carbonic anhydrase inhibitor to a pindolol composition would have a material effect. Buzas demonstrates the synergistic effects, i.e., results greater than the sum of the carbonic anhydrase inhibitor and pindolol taken separately. Moreover, Buzas concludes that the synergistic combination provides "therapeutic effects (reduced secretion parameters) and leads to healing . . . " whereas Buzas fails to draw such a conclusion with regard to pindolol used alone. Instead, Buzas provides only that there is a "slight" decrease in gastric acid secretion and carbonic anhydrase with pindolol alone. Buzas et al. Translation at pages 8 and 11.

Accordingly, the addition of a carbonic anhydrase inhibitor would materially alter a composition "consisting essentially of an effective amount of S(-)pindolol," as recited in the presently claimed invention, by producing a synergistic effect different from the effect of S(-)pindolol alone. Given this synergy, Appellants contend that the addition of carbonic anhydrase inhibitors would materially affect the basic and novel characteristics of the claimed invention. As the Office acknowledges, any elements having such an effect are excluded by a claim that recites, "consisting essentially of." *See* Advisory Action dated June 1, 2004; *see also*, *PPG Industries*, 156 F.3d at 1354, 48 U.S.P.Q.2d at 1353-54.

Thus, carbonic anhydrase inhibitors are properly excluded from the presently amended claims. Nothing in the cited prior art teaches or suggests the use of a

composition that does not include carbonic anhydrase inhibitors. As such, Buzas' disclosures fail to teach or suggest all the claim limitations. *See* M.P.E.P. § 2143.

4. The Office fails to provide a motivation or a reasonable expectation of success for modifying Buzas.

There simply is no clear and particular suggestion in the cited prior art to modify Buzas by omitting a carbonic anhydrase inhibitor from a composition intended for use in treating gastrointestinal disorders. Buzas describes a *synergistic* composition containing a carbonic anhydrase inhibitor and a beta-adrenergic blocker in specific weight ratios. Buzas et al. Translation at page 2. According to Buzas, the object of the invention is to obtain a synergistic composition through the "selection of ingredients and the mixture ratio thereof." *Id.*

In fact, Buzas, as discussed above, suggests that beta-blockers, when used alone, are ineffective as a treatment for duodenal ulcers. *See id.* at page 8, Table 3. Buzas discloses that only after combining the beta-blockers with a carbonic anhydrase inhibitor (acetazolamide or ethoxzolamide) does one achieve a therapeutic effect. *See id.* at page 12, Table 9. Thus, Buzas reports that the combination might be therapeutic, but that beta-blockers alone are not. Buzas fails to provide any guidance to suggest or motivate one of ordinary skill in the art to use a beta-blocker as a mono-therapy for gastrointestinal conditions.

Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. M.P.E.P. § 2146(X) (citing *In re Hedges*, 783 F.2d 1038, 228 U.S.P.Q. 685 (Fed. Cir. 1986)). As discussed in detail above, Buzas clearly shows that beta-blockers alone are an ineffective treatment for duodenal ulcers. Contrary to Buzas'

teaching that only the combination of pindolol and a carbonic anhydrase inhibitor are effective, Appellants show that pindolol alone provides a substantial reduction in average symptom severity in patients suffering from non-ulcerative dyspepsia. Specification at page 7.

Moreover, there is no reasonable expectation of success to support modifying the teachings of Buzas in the manner proposed by the Office. Buzas, as discussed in detail above, suggests that beta-blockers alone are ineffective treatments for the one condition tested (duodenal ulcers). Given such guidance, one skilled in the art would have no reasonable expectation of successfully using pindolol or a sterioisomer of pindolol to treat the same disorder without first proving that Buzas was wrong. Accordingly, for at least these reasons, the Office failed to establish a prima facie case of obviousness and thus, reversal of this rejection is requested.

Conclusion

For the reasons given above, pending claims 1 and 4-7 are allowable and reversal of the Office's rejection is respectfully requested. The use of the transitional phrase "consisting essentially of" excludes the addition of carbonic anhydrase inhibitors taught in Buzas. Without pointing to a suggestion or motivation to modify Buzas' teachings, the Office fails to meet the criteria of a prima facie case of obviousness.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: January 27, 2005

By: _____
Adriana L. Burgy
Reg. No. 48,564

Claims Appendix to Appeal Brief Under Rule 41.37(c)(1)(viii)

1. (Previously Presented) A method for treating gastrointestinal disease comprising administering a composition consisting essentially of an effective amount of S(-) pindolol, or a salt thereof, to a subject in need thereof.

2-3 (Canceled)

4. (Previously Presented) The method according to claim 1, wherein an effective amount of S(-) pindolol, or its salts, is administered in a pharmaceutical dosage form that permits rapid release of the S(-) pindolol.

5. (Previously Presented) The method according to claim 1, wherein an effective amount of the S(-) pindolol, or its salts, is administered in a pharmaceutical dosage form that releases the S(-) pindolol in a slow or controlled fashion.

6. (Previously Presented) The method according to claim 1, wherein the gastrointestinal diseases are selected from non-ulcerative dyspepsia, irritable bowel syndrome, or chemotherapy-associated disorders of motility.

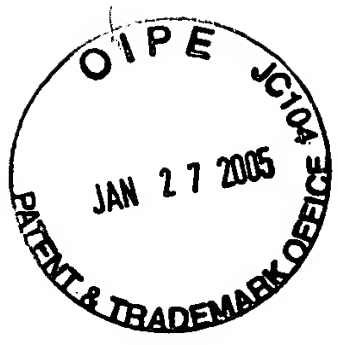
7. (Previously Presented) The method according to claim 6, wherein the chemotherapy-associated disorder of motility is nausea.

Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix)

1. Amendment and Request for Reconsideration under 37 C.F.R. § 1.116 filed on May 6, 2004.

2. Second Amendment and Request for Reconsideration under 37 C.F.R. § 1.116 filed on June 28, 2004.

3. Buzas et al. Translation submitted to the Office in an Information Disclosure Statement with the Response filed on November 13, 2003.



MAB/WLS/MTR/KAT

PLEASE STAMP TO ACKNOWLEDGE RECEIPT OF THE FOLLOWING:

In re Application of: T. G. DINAN et al.

U.S. Patent Application No. 09/687,384 Group Art Unit: 1614

Filed: October 13, 2000 Examiner: Donna A. JAGOE

For: TREATMENT AND PREVENTION OF GASTROINTESTINAL DISEASE USING ANTAGONISTS OR PARTIAL AGONISTS OF 5HT1a RECEPTORS

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1. Amendment and Request for Reconsideration

Dated: May 6, 2004

Docket No.: 09487.0001-00000
Customer No. 22,852

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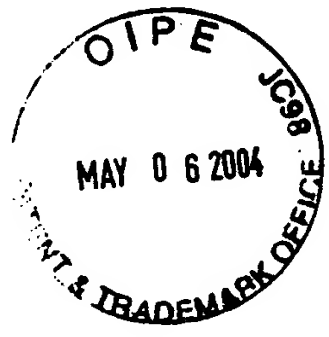

(Due Date: May 26, 2004)

5/7/4

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RESPONSE UNDER 37 C.F.R. § 1.116
EXPEDITED PROCEDURE REQUESTED
EXAMINING GROUP 1647
Attorney Docket No. 09487.0001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Timothy. G. DINAN et al.	)	Group Art Unit: 1614
	)	
Application No.: 09/687,384	)	Examiner: Donna A. JAGOE
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Filed: October 13, 2000	)	
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For: TREATMENT AND PREVENTION OF GASTROINTESTINAL DISEASE USING ANTAGONISTS OR PARTIAL AGONISTS OF 5HT1a RECEPTORS	)	

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT AND REQUEST
FOR RECONSIDERATION UNDER 37 C.F.R. § 1.116

In response to the final Office Action mailed February 26, 2004, Applicants respectfully request reconsideration of the subject application in light of the following remarks.

Amendments to the Claims are included in this paper. **Remarks and Arguments** follow the amendment section of this paper.

AMENDMENTS TO THE CLAIMS:

1. (Currently Amended) A method for treating gastrointestinal disease comprising administering a composition consisting essentially of an effective amount of S(-) pindolol, or a salt thereof, to a subject in need thereof.

2-3. (Canceled)

4. (Previously Presented) The method according to claim 1, wherein an effective amount of S(-) pindolol, or its salts, is administered in a pharmaceutical dosage form that permits rapid release of the S(-) pindolol.

5. (Previously Presented) The method according to claim 1, wherein an effective amount of the S(-) pindolol, or its salts, is administered in a pharmaceutical dosage form that releases the S(-) pindolol in a slow or controlled fashion.

6. (Previously Presented) The method according to claim 1, wherein the gastrointestinal diseases are selected from non-ulcerative dyspepsia, irritable bowel syndrome, or chemotherapy-associated disorders of motility.

7. (Previously Presented) The method according to claim 6, wherein the chemotherapy-associated disorder of motility is nausea.

REMARKS

In the Office Action, the Examiner indicates that claims 1 and 4-7 are pending in this application. With entry of this response, claim 1 is amended and no claims are canceled or added. Thus, claims 1 and 4-7 remain pending.

The Claims Are Not Obvious Over Buzas *et al.*

The Examiner rejects claims 1 and 4-7, under 35 U.S.C. § 103(a), as allegedly being unpatentable over Buzas *et al.* (RO 92436), for the reasons made of record. Office Action, page 2. According to the Examiner, Buzas describes a composition comprising a carbonic anhydrase inhibitor and a beta-blocker to treat gastritis, gastro-duodenitis, and gastro-duodenal ulcers. *Id.*, pages 2-3. In response to Applicants' arguments traversing the obviousness rejection, the Examiner apparently agrees that Buzas is limited to synergistic combinations of carbonic anhydrase inhibitors and certain other specified compounds, including some beta-blockers like pindolol. These teachings concerning combinations do not render obvious a claim that excludes carbonic anhydrase inhibitors. The Examiner, however, contends that the "comprising" language used in Applicants' claims does not exclude the combination of carbonic anhydrase inhibitors and pindolol described by Buzas.

In response, Applicants have amended the claims to recite a composition consisting essentially of (S)-pindolol. The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristics of the claimed invention. M.P.E.P. § 2111.03; *In re Herz*, 537 F.2d 549, 551-52 (C.C.P.A. 1976). Thus, the amended claims exclude carbonic anhydrase inhibitors. And nothing in the cited prior art

teaches or suggests the use of a composition that does not include carbonic anhydrase inhibitors. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 1 and 4-7, under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

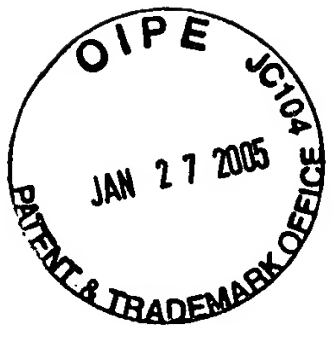
Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: May 6, 2004

By: _____
M. Todd Rands
Reg. No. 46,249

MCD - WLS-MTR - CAT



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U.S. Patent Application No. 09/687,384 Group Art Unit: 1614

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1. Second Amendment and Request for Reconsideration Under 37 C.F.R. § 1.116
2. Notice of Appeal
3. Petition for Extension of Time
4. Check for $440.00 (Petition Fee and Appeal Fee)

Dated: June 28, 2004

Docket No.: 09487.0001-00000
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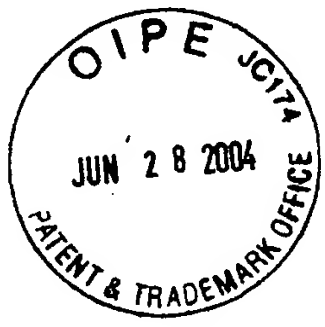

(Due Date: June 28, 2004)

DK 6-29-04

6/29/04

ATTENTION: MAIL STOP AF
RESPONSE UNDER 37 C.F.R. § 1.116
EXPEDITED PROCEDURE REQUESTED
EXAMINING GROUP 1647
Attorney Docket No. 09487.0001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Timothy. G. DINAN et al.	)	Group Art Unit: 1614
	)	
Application No.: 09/687,384	)	Examiner: Donna A. JAGOE
	)	
Filed: October 13, 2000	)	
	)	
For: TREATMENT AND PREVENTION OF GASTROINTESTINAL DISEASE USING ANTAGONISTS OR PARTIAL AGONISTS OF 5HT1a RECEPTORS	)	

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

SECOND AMENDMENT AND REQUEST
FOR RECONSIDERATION UNDER 37 C.F.R. § 1.116

In response to the final Office Action mailed February 26, 2004 ("final Office Action"), and the Advisory Action mailed June 1, 2004 ("Advisory Action"), Applicants respectfully request reconsideration of the subject application in light of the following amendments and remarks. In a separate Petition, Applicants have requested and paid the fee for a one-month extension of time. Because June 26, 2004, is a Saturday, this response is timely filed on Monday, June 28, 2004.

Amendments to the Claims are included in this paper. **Remarks and Arguments** follow the amendment section of this paper.

AMENDMENTS TO THE CLAIMS:

1. (Currently Amended) A method for treating gastrointestinal disease comprising administering a composition consisting essentially of an effective amount of S(-) pindolol, or a salt thereof, to a subject in need thereof.

2-3. (Canceled)

4. (Previously Presented) The method according to claim 1, wherein an effective amount of S(-) pindolol, or its salts, is administered in a pharmaceutical dosage form that permits rapid release of the S(-) pindolol.

5. (Previously Presented) The method according to claim 1, wherein an effective amount of the S(-) pindolol, or its salts, is administered in a pharmaceutical dosage form that releases the S(-) pindolol in a slow or controlled fashion.

6. (Previously Presented) The method according to claim 1, wherein the gastrointestinal diseases are selected from non-ulcerative dyspepsia, irritable bowel syndrome, or chemotherapy-associated disorders of motility.

7. (Previously Presented) The method according to claim 6, wherein the chemotherapy-associated disorder of motility is nausea.

REMARKS

In the Office Action, the Examiner indicates that claims 1 and 4-7 are pending in this application. With entry of this response, claim 1 is amended and no claims are added or canceled. Thus, claims 1 and 4-7 remain pending.

Applicants again request that claim 1 be amended as shown in the claim listing. The Examiner refused Applicants' request filed on May 6, 2004, to enter this amendment, without explanation. Applicants respectfully contend that this amendment "will place the application either in condition for allowance or in better form for appeal" as required. M.P.E.P. 714.12. In fact, the narrower scope of the amended claims focuses the issues for appeal and does not require any new searching by the Examiner. Thus, the amendment can and should be entered.

The fact that the Examiner simply does not believe that the amended claims are patentable is not a reasonable basis for denying the entry of Applicants' amendment. Moreover, if the Examiner refuses to enter this amendment, Applicants will be denied a fair opportunity to appeal the Examiner's interpretation of the "consisting essentially of" claim language as it is being applied to the teachings of Buzas. Accordingly, Applicants have presented the identical claim amendment with this paper and respectfully request that the Examiner enter the amended claims.

The Claims Are Not Obvious Over Buzas *et al.*

In the Advisory Action, the Examiner maintains the rejection of claims 1 and 4-7, under 35 U.S.C. § 103(a), as allegedly being unpatentable over Buzas *et al.* (RO 92436), for the reasons made of record. Advisory Action, page 2. The Examiner previously stated that Buzas describes a composition comprising a carbonic

anhydrase inhibitor and a beta-blocker to treat gastritis, gastro-duodenitis, and gastro-duodenal ulcers. Final Office Action, pages 2-3. The Examiner also argued that Applicants' claims reciting a composition "comprising" (S)-pindolol did not exclude the combination with carbonic anhydrase inhibitors. *Id.*, page 3.

In response to the final Office Action, Applicants amended the claims to exclude the combination of carbonic anhydrase inhibitors and pindolol that is allegedly described by Buzas. The amended claims recite a composition "consisting essentially of an effective amount of S(-) pindolol."[1] The Examiner notes that the language "consisting essentially of" limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristics of the claimed invention. M.P.E.P. § 2111.03 (citing *In re Herz*, 537 F.2d 549, 551-52 (CCPA 1976)). According to the Examiner, "it does not appear that the addition of the carbonic anhydrase inhibitor of Buzas et al. would materially change the characteristics of applicant's invention." Advisory Action, page 2.

Applicants respectfully disagree. Buzas teaches that carbonic anhydrase inhibitors, when used in combination with certain other specified compounds (including some beta-blockers like pindolol), provide a synergistic effect. Buzas' synergistic compositions contain a carbonic anhydrase inhibitor and a beta-adrenergic blocker selected from among propranolol, atenolol, pindolol, timolol, oxprenolol, acebutolol, or metoprolol in a weight ratio of 1.37 to 231. Buzas, page 2. Buzas states, "[t]he object of the present invention is to obtain a synergistic pharmaceutical composition . . .

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[1] As noted above, the Examiner refused to enter this amendment.

[through the] selection of ingredients and the mixture ratio thereof." *Id.* Each of Buzas' claims are also explicitly limited to "synergistic" combinations. Achieving synergy appears to be Buzas' whole basis for describing the use of such combination therapies.

According to Buzas' teachings, the addition of a carbonic anhydrase inhibitor would materially alter a composition "consisting essentially of an effective amount of (S)-pindolol" by producing a synergistic effect different from the effect of (S)-pindolol alone. Given this synergy, Applicants contend that the addition of carbonic anhydrase inhibitors would materially affect the basic and novel characteristics of Applicants' claimed invention. As the Examiner acknowledges, any elements having such an affect are excluded by a claim that recites "consisting essentially of." Thus, carbonic anhydrase inhibitors are properly excluded from the presently amended claims. And nothing in the cited prior art teaches or suggests the use of a composition that does not include carbonic anhydrase inhibitors. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 1 and 4-7, under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: June 28, 2004

By: _____
M. Todd Rands
Reg. No. 46,249

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ROMANIA

NATIONAL COUNCIL FOR SCIENCE AND TECHNOLOGY

STATE PATENT AND TRADEMARK OFFICE

PATENT (19) RO (11) 92436

(12) DESCRIPTION OF THE INVENTION

(21) Application No. 118,467 (22) Filing date: April 19, 1985 (61) Continuation patent application to patent no.: (45) Publication date: September 30, 1987	(51) Int. Cl.[4]: A 61 K 9/20
(86) International application (PCT) No.: Date: (87) International publication: No.: Date: (89)	(30) Priority (32) Date: (33) Country: (31) Certificate no.:

(71) Applicant: (72) Inventors: **Ioan Puşcaş, M.D., Şimleul Silvaniei, district Maramureş; Carmen Puşcaş, M.D., Şimleul Silvaniei, district Maramureş; Gheorghe Buzaş, M.D., Cluj-Napoca; Lucian Sturzu, engineer, Şimleul Silvaniei, district Maramureş.**

(73) Assignee: **Întreprinderea de Medicamente, Bucureşti**

Synergistic pharmaceutical composition for the treatment of gastritis, gastroduodenitis and gastric and duodenal ulcers

(57) Abstract

Synergistic pharmaceutical composition for the treatment of gastritis, gastroduodenitis, and gastric and duodenal ulcers according to the invention comprising in addition to a carbonic anhydrase inhibitor, a *beta*-adrenergic blocker selected from among propranolol, atenolol, pindolol, timolol, oxprenolol, acebutolol or metoprolol having a weight ratio of carbonic anhydrase inhibitor to *beta*-blocker of 1.37 to 231.

Group: 4

Price: 55.48 Lei

(19) RO (11)

Example 5

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.9 acetazolamide, 0.3 sodium bicarbonate, 0.7 potassium bicarbonate, 2.25 magnesium oxide, 0.5 aluminum hydroxide, 0.3 sodium citrate, 0.11 atenolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 8.2.

Example 6

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 1.62 acetazolamide, 0.54 sodium bicarbonate, 1.26 potassium bicarbonate, 4.05 magnesium oxide, 0.9 aluminum hydroxide, 0.54 sodium citrate, 0.023 atenolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 70.4.

Example 7

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.37 ethoxzolamide, 1.15 potassium bicarbonate, 2.5 magnesium oxide, 0.625 aluminum hydroxide, 0.5 sodium citrate, 0.125 atenolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 2.9.

Example 9 [sic] [8]

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.666 ethoxzolamide, 2.07 potassium bicarbonate, 4.5 magnesium oxide, 1.125 aluminum hydroxide, 0.9 sodium citrate, 0.017 atenolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 39.2.

Example 9

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.9 acetazolamide, 0.3 sodium bicarbonate, 0.7 potassium bicarbonate, 2.25 magnesium oxide, 0.5 aluminum hydroxide, 0.3 sodium citrate, 0.03 pindolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 30.

Example 10

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 1.26 acetazolamide, 0.54 sodium bicarbonate, 1.26 potassium bicarbonate, 4.05 magnesium oxide, 0.9 aluminum hydroxide, 0.54 sodium citrate, 0.01 pindolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 162.

Example 11

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.37 ethoxzolamide, 1.15 potassium bicarbonate, 2.5 magnesium oxide, 0.625 aluminum hydroxide, 0.5 sodium citrate, 0.028 pindolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 13.2.

Example 12

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.666 ethoxzolamide, 2.07 potassium bicarbonate, 4.5 magnesium oxide, 1.125 aluminum hydroxide, 0.9 sodium citrate, 0.007 pindolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 95.1.

Example 13

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.9 acetazolamide, 0.3 sodium bicarbonate, 0.7 potassium bicarbonate, 2.25 magnesium oxide, 0.5 aluminum hydroxide, 0.3 sodium citrate, 0.023 timolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 39.1.

Example 14

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 1.62 acetazolamide, 0.54 sodium bicarbonate, 1.26 potassium bicarbonate, 4.05 magnesium oxide, 0.9 aluminum hydroxide, 0.54 sodium citrate, 0.007 timolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 231.

Example 15

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.37 ethoxzolamide, 1.15 potassium bicarbonate, 2.5 magnesium oxide, 0.625 aluminum hydroxide, 0.5 sodium citrate, 0.017 timolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 21.8.

Example 16

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.666 ethoxzolamide, 2.07 potassium bicarbonate, 4.5 magnesium oxide, 1.125 aluminum hydroxide, 0.9 sodium citrate, 0.003 timolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 222.

Example 17

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.9 acetazolamide, 0.3 sodium bicarbonate, 0.7 potassium bicarbonate, 2.25 magnesium oxide, 0.5 aluminum hydroxide, 0.3 sodium citrate, 0.057 oxprenolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 15.8.

Example 18

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 1.26 acetazolamide, 0.54 sodium bicarbonate, 1.26 potassium bicarbonate, 4.01 magnesium oxide, 0.9 aluminum hydroxide, 0.54 sodium citrate, 0.015 oxprenolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 108.

Example 19

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.37 ethoxzolamide, 1.15 potassium bicarbonate, 2.5 magnesium oxide, 0.625 aluminum hydroxide, 0.5 sodium citrate, 0.063 oxprenolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 5.8.

Example 20

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.666 ethoxzolamide, 2.07 potassium bicarbonate, 4.5 magnesium oxide, 1.125 aluminum hydroxide, 0.9 sodium citrate, 0.017 oxprenolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 39.2.

Example 21

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.9 acetazolamide, 0.3 sodium bicarbonate, 0.7 potassium bicarbonate, 2.25 magnesium oxide, 0.5 aluminum hydroxide, 0.3 sodium citrate, 0.32 acebutolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 2.8.

Example 22

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 1.62 acetazolamide, 0.54 sodium bicarbonate, 1.26 potassium bicarbonate, 4.05 magnesium oxide, 0.9 aluminum hydroxide, 0.54 sodium citrate, 0.18 acebutolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 9.

Example 23

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.37 ethoxzolamide, 1.15 potassium bicarbonate, 2.5 magnesium oxide, 0.625 aluminum hydroxide, 0.5 sodium citrate, 0.27 acebutolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 1.37.

Example 24

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.666 ethoxzolamide, 2.07 potassium bicarbonate, 4.5 magnesium oxide, 1.125 aluminum hydroxide, 0.9 sodium citrate, 0.18 acebutolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 3.7.

Example 25

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.9 acetazolamide, 0.3 sodium bicarbonate, 0.7 potassium bicarbonate, 2.25 magnesium oxide, 0.5 aluminum hydroxide, 0.3 sodium citrate, 0.12 metoprolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 7.5.

Example 26

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 1.62 acetazolamide, 0.54 sodium bicarbonate, 1.26 potassium bicarbonate, 4.05 magnesium oxide, 0.9 aluminum hydroxide, 0.54 sodium citrate, 0.34 metoprolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 47.6

Example 27

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.37 ethoxzolamide, 1.15 potassium bicarbonate, 2.5 magnesium oxide, 0.625 aluminum hydroxide, 0.5 sodium citrate, 0.13 metoprolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 2.8.

Example 28

To obtain the pharmaceutical product, mix the following ingredients (amounts are expressed in mmol): 0.666 ethoxzolamide, 2.07 potassium bicarbonate, 4.5 magnesium oxide, 1.125 aluminum hydroxide, 0.9 sodium citrate, 0.03 metoprolol. The molar ratio of sulfonamide inhibitor to *beta*-adrenergic blocker is 22.2.

Carbonic anhydrase represents an essential phase in determining the rate of the gastric acid secretion process. Inhibiting gastric secretion through various inhibitors leads to reduced hydrochloric acid production, thus creating the necessary conditions for the healing of the gastroduodenal mucosa damaged by hydrochloric acid and peptin.

The gastric acid secretion process occurs in the gastric glands in the fundic area of the gastric mucosa and is controlled by a combination of neural, hormonal and food stimuli.

Hydrochloric acid is produced in the parietal cells the main stimuli being gastrin, acetylcholine and histamine. For these secretagogues, specific receptors at the level of parietal cells have been posited and identified.

It is assumed that adrenergic stimulation (adrenaline, noreadrenaline, isoprenaline, etc.) occurs at the level of specific receptors grafted on parietal cells, however, the existence and identification of such receptors has not been experimentally demonstrated.

Currently, anatomically and pharmacologically defined adrenergic receptors are divided into *alfa* and *beta*-receptors; when the response to a series of agonists consists of the succession adrenaline – noreadrenaline – isoproterenol (isoprenaline) – *alfa* receptors, and (isoproterenol) – noreadrenaline – adrenaline – *beta*-receptors, respectively.

In vitro studies of the effect of adrenergic agonists on the activity of purified, human red blood cell and gastric mucosa carbonic anhydrase have shown, first, a strong activating effect of isoprenaline on enzyme activity, and second, a *beta*-adrenergic receptor behavior (table 1).

The effect of adrenergic agonists on the activity of purified, red blood cell [RBC], *and human gastric mucosa (GM) carbonic anhydrase* [CA]

Concentration (M)	Isoprenaline			Orciprenaline	Adrenaline	Noradrenaline
	Pure CA	RBC	MG	Pure CA	Pure CA	Pure CA
0	2040	2572	1.96	2088	2060	2094
10^{-8}	2040	2680	1.96	2047	2040	2136
10^{-7}	2125	2662	1.95	2033	2081	2122
10^{-6}	2168	2736	1.96	2047	2109	2122
10^{-5}	2416	2699	1.96	2518	2225	2122
10^{-4}	3076	3051	2.46	3295	2181	2136
$2 \cdot 10^{-4}$			2.81		2255	
$2 \cdot 10^{-4}$					2428	
$4 \cdot 10^{-4}$					2562	
$5 \cdot 10^{-4}$			3.33		2528	
$1 \cdot 10^{-3}$ 4083		4558	4.12			2164
$2 \cdot 10^{-3}$ 5425		7358	5.73			

The study of the effect of some *beta*-adrenergic blockers such as propranolol, timolol, oxprenolol, pindolol, atenolol, metoprolol or practolol indicated a strong inhibiting action on the activity of purified, human red blood cell and gastric mucosa carbonic anhydrase (table 2).

Table 2

The effect of some beta-adrenergic blockers on the activity of pure [sic], *red blood cell* [RBC], *and human gastric mucosa (GM) carbonic anhydrase (CA)*

Concentration (M)	Propranolol		GM	Pindolol		Atenolol		MC [sic] [GM]	Timolol		Propranolol Pure CA	Acebutolol Practelol [sic] Pure CA	Metoprolol Pure CA
	Pure CA	RBC		RBC	GM	Pure CA	RBC		Pure CA	GM			
10^{-8}	2047 2047	3328	2.07	3624 3672	1.91 1.53	2077 2072	3492 3378	1.04	2048 2034	1.06 1.05	1966 2047	1993 1999	1959 2000
10^{-7}	2075	3328	2.05	3648	1.92	2106	3492		2000	1.05	1889	1980	2041
10^{-6}	2075	3284	2.07	3672	1.52	2034	3539		2006	1.04	1966	1927	2055
10^{-5}	2006	3175	2.04	2061	1.37	2135	3635		2020	1.03	1915	1877	2055
10^{-4}	1716	2777	1.91			1979	3635	1.05	1809	0.98	1779	1720	2027
$2 \cdot 10^{-4}$	1636	2221	1.28						1530	0.98			
$3 \cdot 10^{-4}$	1338	1126	1.09						1299	0.93			
$3 \cdot 4 \cdot 10^{-4}$	1211	1079	1.06			1759		0.99			1300		
$5 \cdot 10^{-4}$						1618	2064	0.86	1023	0.80	1100	1186	1408
10^{-3}													
$4 \cdot 10^{-3}$												952	
10^{-2}													

In vivo administration of some *beta*-adrenergic blockers to patients with gastroduodenal disorders leads to slightly decreased gastric acid secretion parameters and carbonic anhydrase activity (table 3).

Table 3

The effect of some beta-adrenergic blockers on the production of hydrochloric acid and on the activity of [human] *gastric mucosa (GM) and red blood cell* [RBC] *carbonic anhydrase (CA) in patients with duodenal ulcers after three days of treatment*

Beta-blocker	Nos. of cases	Dose mg/day	H+ Flow mEq/h	CA	
				GM	RBC
Control group	29	-	9.87 ± 2.71	1.87 ± 0.13	2876 ± 139
Propranolol	20	3 × 20	7.27 ± 1.82	1.62 ± 0.35	2514 ± 275
Pindolol	20	3 × 10	7.98 ± 1.17	1.70 ± 0.31	2590 ± 113
Practolol	20	3 × 200	6.89 ± 1.65	1.58 ± 0.39	2476 ± 326
Oxprenolol	20	3 × 20	7.14 ± 0.98	1.67 ± 0.19	2623 ± 170
Metoprolol	20	3 × 10	6.97 ± 1.82	1.76 ± 0.27	2768 ± 123
Atenolol	20	3 × 10	7.45 ± 1.63	1.79 ± 0.33	2796 ± 273
Timolol	20	3 × 20	7.16 ± 2.08	1.71 ±0.29	2783 ± 315

In vitro study of the interaction between adrenergic agonists and acetazolamide, a carbonic anhydrase specific inhibitor, which operates at the active-site level through zinc ion chelation, proves the existence of a noncompetitive antagonism and indicates the fact that adrenergic agonists do not operate at the level of the zinc atom.

Table 4

The interaction between adrenergic agonists and acetazolamide on the activity of purified carbonic anhydrase

Concentration (M)	Acetazolamide	Isoprenaline	Isoprenaline + Acetazolamide 10^{-8} M	Isoprenaline + Acetazolamide 10^{-7} M	Isoprenaline + Acetazolamide 10^{-4} M
0	2061	2047	2020	2000	2040
10^{-9}	2047	2131	1754	631	536
10^{-8}	1742	2189	1851	660	552
10^{-7}	608	2189	1851	666	552
10^{-6}	563	2264	1839	702	602
10^{-5}	557	2372	1876	804	643
10^{-4}	514	2814	2047	893	696
10^{-3}	493	3940	2776	1656	994

In vitro study of the interaction between adrenergic agonists and histamine, a strong carbonic anhydrase activator, indicates the existence of a noncompetitive synergism (table 5).

Table 5

The interaction between adrenergic agonists and histamine on the activity of pure [sic] *carbonic anhydrase*

Concentration (M)	Histamine	Isoprenaline	Histamine + Isoprenaline 10^{-6} M	Histamine + Isoprenaline 10^{-5} M	Histamine + Isoprenaline 10^{-1} M
10^{-8}	1993	1993	2020	2006	2020
10^{-8}	2191	--	2104	2361	3237
10^{-7}					
10^{-6}	2377	2147	2377	2361	3372
10^{-5}	2510	2377	2546	2528	3575
10^{-4}	2690	2904	2785	2617	3655
10^{-3}	2824	--	2925	3184	3794
10^{-2}	3910	--	3822	4156	4494

In vitro study of the activity of carbonic anhydrase indicates that *beta-adrenergic* blockers interacting with acetazolamide promote noncompetitive synergism (table 6), with histamine noncompetitive antagonism (table 7), and with isoprenaline competitive antagonism (Table 8).

Table 6

The interaction between beta-adrenergic blockers and acetazolamide on the activity of purified carbonic anhydrase

Concentration (M)	Propranolol	Acetazolamide	Propranolol + Acetazolamide 10^{-8} M	Propranolol + Acetazolamide 10^{-7} M	Propranolol + Acetazolamide 10^{-6} M
0	2068	2081			
10^{-8} M		1833			
10^{-7} M		875			
10^{-6} M		445			
10^{-4} M	1657		1517	755	214
$2 \cdot 10^{-4}$ M	1417		1164	425	0
$3 \cdot 10^{-4}$ M	1139		938	300	0
$3 \cdot 38 \cdot 10^{-4}$ M	953		807	243	0

Table 7

The interaction between beta-adrenergic blockers and histamine on the activity of purified carbonic anhydrase

Concentration (M)	Atenolol	Propranolol	Histamine	Histamine + Propranolol $2 \cdot 10^{-4}$	Histamine	Histamine + Propranolol 10^{-3}
0	2074	1967	1980	1993	2102	2074
10^{-8}	2173		2288	1759	2246	1710
10^{-7}	2088		2303	1724	2417	1906
10^{-6}	2102	2511	2511	1747	2656	2022
10^{-5}	2088		2720	2033	2843	2140
10^{-4}	1954		2872	2101	2962	2104
$2 \cdot 10^{-4}$		1440				
10^{-3}	1733		3010	2334	3110	2246
10^{-2}			3972	3389	4153	3557

Table 8

The interaction between beta-adrenergic blockers and isoprenaline on the activity of pure [sic] *carbonic anhydrase*

Concentration (M)	Atenolol	Isoprenaline	Orciprenaline	Atenolol + +Isoprenaline	Atenolol + + Orciprenaline
0	2000	2040	2054	2040	2040
10^{-8}	2139	2125	2068	2153	2168
10^{-7}	2082	2110	2197	2197	2139
10^{-6}	1946	2227	2242	2082	2168
10^{-5}	1920	2400	2351	2082	2242
10^{-4}	1882	2846	2809	2432	2569
$1.6 \cdot 10^{-4}$			2929		2096
10^{-3}	1633	4000		3076	
$4 \cdot 10^{-3}$	669				

Table 8 (continuation)

Concentration (M)	Atenolol	Isoprenaline	Isoprenaline + +Atenolol $5 \cdot 10^{-4}$ M	Isoprenaline + + Atenolol $8 \cdot 10^{-4}$ M
0	3492	3416	3469	3492
10^{-8}	3378	3708	2716	2475
10^{-7}	3492	3733	2826	2593
10^{-6}	3539	3683	2845	2593
10^{-5}	3635	3912	2921	2864
10^{-4}	3635	4073	3446	3039
$5 \cdot 10^{-4}$	2735	-	-	-
$8 \cdot 10^{-4}$	2426	-	-	-
10^{-3}	2064	5868	4938	4575
$2.36 \cdot 10^{-3}$	-	6619	6044	5911

These results indicate the fact that carbonic anhydrase acts as an adrenergic *beta*-receptor and could be the binding site of adrenergic agonists based on their secretory effect on gastric acid secretion.

I*n vivo* combined administration of carbonic anhydrase inhibitors and *beta*-adrenergic blockers to patients with gastroduodenal disorders has therapeutic effects (reduced secretion parameters) and leads to healing using reduced inhibitor doses (table 9).

Table 9

The effect of beta-adrenergic blockers combined with acetazolamide or ethoxzolamide on acid gastric secretion parameters in patients with duodenal ulcers after three days of treatment

Name	Nos. of cases	Dose mg/day	Flow mEq/h	CA	
				Concentration mEq/l	Volume ml/h
Control group	20	-	9.87 ± 2.71	76 ± 22	129 ± 27
Acetazolamide	20	3 × 600	4.39 ± 1.12	45 ± 12	97 ± 37
Ethoxzolamide	20	3 × 100	3.87 ± 0.98	37 ± 17	105 ± 28
Propranolol	20	3 × 200	7.27 ± 1.82	61 ± 21	119 ± 31
Practolol	20	3 × 200	6.89 ± 2.65	57 ± 28	120 ± 22
Pindolol	20	3 × 10	7.98 ± 2.17	69 ± 22	115 ± 17
Acetazolamide	20	3 × 600	1.89 ± 0.4	27 ± 5	70 ± 13
Propranolol	-	3 × 20			
Acetazolamide+ + Practolol	20	3 × 600	0.87 ± 0.12	19 ± 4	46 ± 15
Acetazolamide	20	3 × 600	0.62 ± 0.31	21 ± 5	29 ± 17
Pindolol	-	3 × 10			
Ethoxzolamide + Propranolol	20	3 × 100 3 × 20	1.12 ± 0.27	26 ± 7	43 ± 11
Ethoxzolamide+ + Practolol	20	3 × 100 3 × 200	0.47 ± 0.09	17 ± 6	27 ± 14
Ethoxzolamide + Pindolol	20	3 × 100 3 × 10	0.71 ± 0.17	24 ± 3	29 ± 7

The composition according to the invention has the following advantages:

-- it allows a 10 to 50% reduction of the effective sulfonamide inhibitor dose;
-- it is well tolerated by the body and it causes no side effects.

Claims

1. Synergistic pharmaceutical composition for the treatment of gastritis, gastroduodenitis, and gastric and duodenal ulcers comprising a carbonic anhydrase inhibitor selected from among sodium acetazolamide, potassium bicarbonate, [TN: word appears to be missing] oxide, or ethoxzolamide combined with sodium bicarbonate, potassium bicarbonate, magnesium oxide, aluminum hydroxide and sodium citrate, **characterized in that** in order to obtain superior therapeutic effects and reduce the anhydrase inhibitor dose said composition comprises in addition to the carbonic anhydrase inhibitor also a *beta*-adrenergic blocker selected from among propranolol, atenolol, pindolol, timolol, oxprenolol,

acebutolol or metoprolol having a weight ratio of carbonic anhydrase inhibitor to *beta*-blocker of 1.37 : 231.

2. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is acetazolamide and the *beta*-adrenergic blocker used is propranolol, the weight ratio thereof is 6 to 81.
3. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is ethoxzolamide and the *beta*-adrenergic blocker used is propranolol, the weight ratio thereof is 2.10 to 29.
4. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is acetazolamide and the *beta*-adrenergic blocker used is atenolol [sic], the weight ratio thereof is 8.2 to 70.4.
5. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is ethoxzolamide and the *beta*-adrenergic blocker used is atenolol, the weight ratio thereof is 2.9 to 39.2.
6. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is acetazolamide and the *beta*-adrenergic blocker used is pindolol, the weight ratio thereof is 30 to 126.
7. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is ethoxzolamide and the *beta*-adrenergic blocker used is pindolol, the weight ratio thereof is 13.2 to 95.1.
8. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is acetazolamide and the *beta*-adrenergic blocker used is timolol, the weight ratio thereof is 39.1 to 231.
9. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is ethoxzolamide and the *beta*-adrenergic blocker used is timolol, the weight ratio thereof is 21.8 to 222.
10. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is acetazolamide and the *beta*-adrenergic blocker used is oxprenolol, the weight ratio thereof is 15.8 to 108.
11. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is ethoxzolamide and the *beta*-adrenergic blocker used is oxprenolol, the weight ratio thereof is 5.8 to 39.2.
12. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is acetazolamide and the *beta*-adrenergic blocker used is acebutolol, the weight ratio thereof is 2.8 to 9.
13. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is acetazolamide and the *beta*-adrenergic blocker used is acebutolol, the weight ratio thereof is 1.37 to .7.
14. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is acetazolamide and the *beta*-adrenergic blocker used is metoprolol, the weight ratio thereof is 7.5 to 47.6.
15. Synergistic pharmaceutical composition according to claim, 1 **characterized in that** if the carbonic anhydrase inhibitor used is acetazolamide and the *beta*-adrenergic blocker used is metoprolol, the weight ratio thereof is 2.8 to 22.2.

(56) Bibliography

R.S.R. patents nos. 65972; 82715; 65969

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Related Proceedings Appendix to Appeal Brief Under Rule 41.37(c)(1)(x)

None